

## DETAILED ACTION

### *Specification*

The disclosure is objected to because of the following informalities: paragraph 39 should be changed in the same manner as paragraph 108. That is, “outside” should be replaced by --inside--.

Appropriate correction is required.

It is noted that Applicant has amended paragraph 108 and claim 45 to replace “outside” with “inside”. (This change needs to be made to paragraph 39 as well.) Applicant asserts that this change corrects a typo and is supported by the disclosure of Fig. 2C. Examiner finds that this correction appears to be consistent with the description of the device, for instance in claim 45, part (vi), reciting “confining means positioned in the chamber to form a confinement region to confine the biological cells therein with the liquid medium”. Since “seed biological cells” are also biological cells, the change from “for allowing seed biological cells to perfuse only *outside* the confined region in the chamber” (emphasis added) to “for allowing seed biological cells to perfuse only *inside* the confined region in the chamber” (emphasis added) appears to be consistent with the purpose of the device and part (vi) of claim 45, and thus Examiner finds that the correction does not appear to add new matter but was intended to be part of the original disclosure but for a typo.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 45 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 45 recites in line 19, "the plane of the first substrate". Since any object is a three dimensional object, and thus has more than one plane, it is not clear as to which plane of the first substrate Applicant refers. For examination purposes, the claim reads on any plane of the first substrate.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 44-49 and 58-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feder et al., 4,201,845.

As to independent claims 44 and 45, Feder et al. teach a device comprising two parts (12 and 13) of a housing (11) secured together to define a chamber (23) within the housing (col. 3, line 13-18) and including a lower filter (40) which serves to distribute the upward fluid flow, and upper filter (41) which prevent cells from passing through the outlet port (col. 6, lines 1-8.) Part (12) is equivalent to Applicant's claimed first substrate, and the upper filter (41) which prevents cells from passing through is equivalent to Applicant's claimed confining means. The Feder et al. device also comprises inlets (26 and 27) and outlet 28) (see fig. 2). Inlets (26 and 27) comprise ports (openings) and thus are equivalent to Applicant's claimed inlet port and first connection channel, and first alternate port and third connection channel, respectively. Outlet port (28) is equivalent to Applicant's claimed outlet port and second connection channel. It is noted that claim 45 recites in line 2 that the first substrate has a first surface and an opposite second surface. The outlet port (28) is on an opposite, second surface (13) from a first surface (12). Furthermore, as to claim 44, the confining means include a first filter (40) proximate to the first connection channel, and second filter (41) proximate to the second connection channel, and the first filter and second filter are substantially parallel to each other (see figure 4), and wherein each of the first filter and second filter comprises a plurality of posts (i.e., the elements forming the filter) spaced apart from each other not

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to allow biological cells to pass through it (see column 5, line 64 - column 6, line 8, disclosing that microporous filter plate (40) preferably has a pore size ranging from about 0.5 to about 10 microns and that lower filter (40) serves as the distributor plate means while upper filter (41) serves as a diffusion barrier to prevent cells from passing through the outlet port and to stop back-flow of spent media, and that the pores of the upper filter is preferably from about 10 to about 100 microns; it is understood that the lower filter (40), having the same or smaller pore size, also serves to prevent cells from passing through the outlet port.)

However, Feder et al. do not teach the in operation the stream of substance flows from the inlet port through the first connection channel, the chamber and the second connection channel to the outlet port in a direction that is substantially parallel to a plane of the first substrate. Rather, the Feder et al. inlet is perpendicular to the outlet and second connection channel. However, modifying the Feder et al. device such that the inlet (and thus first connection channel) is at the bottom of substrate (12), e.g., coaxial with the outlet or otherwise parallel to the vertical plane of the device as shown in figure 4, would have been within the skills of the ordinary artisan as such modification involves only a change in the configuration or shape of the device without departing from the basic concepts of the Feder et al. invention. The skilled artisan would have recognized that such mere change in configuration or shape without departing from the basic concepts of an invention is a design choice that can be varied as desired. Moreover, Feder et al. state that “[i]t will be appreciated that the cell culture reactor of this invention is not limited to the foregoing specific dimensions as other configurations

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will be apparent from the disclosure herein" (col. 4, lines 35-38.) Feder et al. also state that "[i] will be appreciated that many other modifications and variations can be made to the particular embodiments of the invention described hereinbefore without departing from the basic and novel concepts of the invention. For example, other ports such as overflow ports or additional access and feed ports can be provided in the reactor at various convenient locations in the reactor walls" (col. 7, lines 45-52.) Thus, Feder et al. also recognize that a change in configurations or other modifications such as additional ports can be made without departing from the basic concepts disclosed.

As to claims 46 and 58, Feder et al. disclose the invention substantially as claimed except for the first substrate being fabricated from glass or a polymer. Feder et al. describes the first substrate structure (12) (col. 3, line 19) does not mention what material forms the first substrate. However, glass or a polymer would have been obvious to the skilled artisan because Feder et al. disclose in the background that glass or plastic are known to be used for culturing cells (col. 1, lines 18-22), and also another part of the disclosed device may be made of a polymer. Thus, it would have been predictable to the skilled artisan that glass or plastic are compatible materials that may be used to form the structure (12) generally disclosed by Feder et al.

As to claims 47 and 59, Feder et al. do not teach a second substrate sized such that when the second substrate is received by the first substrate, the chamber is covered. Rather, Feder et al. teach that element (13) is fitted to element (12) (see fig. 2). However, modifying the configuration, or adding a removable side to element (12), such as making wall (16) be removable and attachable in a similar manner as element

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(13) involves only a change in the configuration or shape of the device without departing from the basic concepts of the Feder et al. invention. The skilled artisan would have recognized that such mere change in configuration or shape without departing from the basic concepts of an invention is a design choice that can be varied as desired, and Feder et al. also acknowledges the same (col. 4, lines 35-38, and col. 7, lines 45-52.)

As to claims 48 and 60, element (37) is a supporting member outside the confined region of the chamber for supporting element (13) (see figure 2). The skilled artisan would have recognized that this same feature can also be provided in the second substrate discussed in claim 59 for the same purpose, i.e., for supporting the second substrate.

As to claims 49 and 61, the device comprises a lip on the inside of element (12) which is inside the confined region of the chamber and supports the second substrate (13), see fig. 2 and also figure 3). The skilled artisan would have recognized that this same feature can also be provided in the second substrate discussed in claim 59 for the same purpose, i.e., for supporting the second substrate.

As to claim 62, a stream of substance is capable of being controlled as to provide a gradient to the channel, since the flow of fluid introduced can be controlled. It is noted that the stream of substance is not recited as being part of the device and that claim 62 claims a device rather than a method claim. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior

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art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Likewise, as to claims 63 and 64, the stream of substance, or chemokine, or substance affecting the growth of biological cells, is not recited as part of the claimed device but is recited as part of the intended use of the device. The Feder et al. device is capable of allowing chemokine or a substance affecting the growth of biological cells to flow through the device. This is also shown in column 6, line 31, describing a culture medium inlet tube.

Claim 65 recites “wherein sidewalls at the intersections of the first connection channel with the chamber and the second connection channel with the chamber are tapered to form an angle of inclination between about 10-45 degrees from vertical and an enclosed angle between about 30-80 degrees”. Tapering of the walls involves only a change in the configuration or shape of the device without departing from the basic concepts of the Feder et al. invention. The skilled artisan would have recognized that such mere change in configuration or shape without departing from the basic concepts of an invention is a design choice that can be varied as desired, and Feder et al. also acknowledges the same (col. 4, lines 35-38, and col. 7, lines 45-52.)

### ***Response to Arguments***

Applicant's arguments filed March 12, 2008 have been fully considered.

Applicant's clarification as to the meaning of the term “seed” cells is acknowledged, and

Examiner finds that the meaning is clear or at least has been clarified by Applicant as stated in the response of March 12, 2008.

Applicant's remaining arguments however are not persuasive.

Applicant emphasize that Feder et al. disclose a macroscopic device and that the present invention in one embodiment is a microfluidic device. Examiner notes however that "microfluidic" is not recited in the claims and that in any case, miniaturization would have been obvious as microfabrication methods to miniaturize assay device are well known and its benefits are also well known (for example, less reagents are required.)

Applicant also argues that Feder et al. do not disclose the newly added limitations. This argument is moot as the grounds for rejection has been amended as necessitated by the new limitations. Accordingly, the additional limitations of the dependent claims have also been amended. New claim 65 is also addressed above.

It is noted that claim 44 and its dependent claims were previously indicated as having allowable subject matter. However, upon review, claim 44 reads on the disclosure of Feder et al. as stated above in the present Office action. More specifically, as to claim 44, the confining means include a first filter (40) proximate to the first connection channel, and second filter (41) proximate to the second connection channel, and the first filter and second filter are substantially parallel to each other (see figure 4), and wherein each of the first filter and second filter comprises a plurality of posts (i.e., the elements forming the filter) spaced apart from each other not to allow biological cells to pass through it (see column 5, line 64 - column 6, line 8, disclosing that microporous filter plate (40) preferably has a pore size ranging from about 0.5 to about 10 microns



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and that lower filter (40) serves as the distributor plate means while upper filter (41) serves as a diffusion barrier to prevent cells from passing through the outlet port and to stop back-flow of spent media, and that the pores of the upper filter is preferably from about 10 to about 100 microns; it is understood that the lower filter (40), having the same or smaller pore size, also serves to prevent cells from passing through the outlet port.)

Lastly, Examiner notes that the previous Office action stated that element (13) in the Feder et al. patent is equivalent to Applicant's claimed second substrate sized such that when the second substrate is received by the first substrate, the chamber is covered. This was stated in error as element (13) is actually considered to be part of the first substrate. Thus the grounds for rejection has been amended above regarding the second substrate.

### ***.Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Ann Y. Lam/

Primary Examiner, Art Unit 1641